How to monitor early cystic fibrosis lung disease. by multiple-breath washout, chest computed tomography, or both?

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DOI: https://doi.org/10.1164/rccm.201509-1862ED

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How to Monitor Early Cystic Fibrosis Lung Disease

By Multiple-Breath Washout, Chest Computed Tomography, or Both?

The AREST CF (Australian Respiratory Early Surveillance Team for Cystic Fibrosis) program has taught us what every physician caring for young patients with cystic fibrosis (CF) should be aware of: early lung disease may progress while patients are asymptomatic (1). A close relationship among infection, inflammation, lung function, and imaging suggests a real association between measures (2), a necessary point considering the possibility of therapeutic interventions. Such a structure–function relationship between multiple-breath washout (MBW) and computed tomography (CT) scans has already been demonstrated in older children and adults with CF (3, 4) and primary ciliary dyskinesia (5). Whether this also holds true for children aged below 6 years, and which outcome to use preferentially during clinical follow-up and as study endpoint, is unclear as yet.

In this regard, the article in this issue of the *Journal* by Ramsey and colleagues (pp. 60–67) is novel, as it describes for the first time the structure–function relationship between MBW and CT across the whole pediatric age range and in a large cohort of 119 children with 149 paired measurements (6). In contrast to previous studies, the vast majority of the participants in this study had been diagnosed by newborn screening, and thus timely care was provided from infancy on. The primary outcomes were the PRAGMA-CF (Perth-Rotterdam Annotated Grid Morphometric Analysis for CF) score from CT scans and the lung clearance index (LCI) from MBW measurements. Abnormal LCI predicted presence of bronchiectasis with around 85% probability in preschool and school-aged children. In infants, the positive predictive value of abnormal LCI, however, was only 18%. Comparably, a significant association between various MBW outcomes and different CT scores, including overall extent of disease and air trapping, was found only in preschool and school-aged children, whereas in infants, the association was weak.

The results in preschool and school age are in line with previous data, suggesting that LCI in these age groups can be used to detect or, even more important, exclude bronchiectasis and trapped gas (3, 4). The lack of an association in infancy, however, raises some questions about underlying reasons and its meaning for clinical practice and future intervention trials.

CT scans are considered a robust proxy for structural CF lung disease. However, there is no generally accepted gold standard to define the extent of clinically relevant lung disease. Although interrater agreement of CT scores is good, intertest variability of CT scans is ethically impossible to assess in humans. Theoretically, the extent of lung disease could be overestimated in CT scans in infants. Inspiratory CT scans were obtained at an airway opening pressure of 25 cm H_2O. Although detection of bronchiectasis is certainly improved, physiological surrogate outcomes in infant lungs, such as trapped air, are likely influenced as well. No healthy controls were tested in the youngest age group up to 3 years, neither for MBW nor for CT scans (6). Thus, the exact specificity of trapped air from CT scans for CF lung disease remains unknown. In addition, effects of sedation, body posture, and breathing pattern are age-dependent and interact with ventilation efficiency in a complex way (7, 8).

Some pieces in the "LCI puzzle" are also missing. For example, does an elevated LCI value despite normal CT suggest a "false-positive" finding? Abnormal LCI depends on appropriate normative data, which are unfortunately scarce throughout childhood. Further, associations do not suggest any chronological or causal order. We do not know yet whether elevated LCI precedes or lags behind bronchiectasis, hyperinflation, mucus plugs, air trapping, or poorly ventilated lung areas, and to which extent the LCI is exactly influenced by one or a combination of the latter pathologies. Again, a rather complex dynamic interaction must be assumed, as, for example, recent studies did not show clear improvements in LCI after intravenous antibiotic treatment, despite improvements in spirometry (9, 10). If poorly ventilated areas of the lung are opened up during therapy, hyperinflation decreases, but LCI may increase (10). Further, ventilation inhomogeneity and/or air trapping must be subject to change over time. Thus, outcome measures are likely to show a dynamic behavior, especially during infancy, where breathing pattern and thorax rigidity are less stable than at later age. Likewise, bronchiectasis can only be detected by MBW if established over time and existent to a certain degree. One could even imagine a certain threshold in bronchiectasis above which LCI turns abnormal.

CT and MBW measurements and analysis algorithms are subject to constant improvements, and thus hardware and software changes may influence outcomes (11, 12). In this regard, the study has some weaknesses. Despite the use of newest software algorithms for MBW analysis (13), the temperature model applied during analysis is validated for infants up to 10 weeks only (14), but

was used in the current paper in children up to 3 years (6). Different LCI results compared with recent publications of the same cohort underline the susceptibility of MBW to hardware and software changes (2).

Further, the sensitivity of any parameter depends on the prevalence of the gold standard. In this study, the occurrence and extent of the gold standard "air trapping" on CT scans is extremely low in infancy (e.g., mean extent of air trapping, 1.3%). Thus, it is not surprising, from a statistical point of view, that the association is not robust. From a clinical and physiological point of view, it raises the question of what that extent of air trapping actually means.

So what do the current results tell us for future studies and clinical practice after newborn screening? To not perform MBW, but only CT, in infancy? To not perform radiological assessments after children have reached preschool age? At school age, to only rely on MBW to detect bronchiectasis and air trapping?

To address some of those questions, we believe the following points need to be studied further. First, interventional trials using MBW as outcome need to be combined with conventional lung function tests, including bodyplethysmography. Otherwise, the effect of hyperinflation on MBW results cannot be understood (10). Second, future infant studies should include matched healthy controls to avoid extrapolation of reference equations (15). Third, manufacturers of commercially available equipment and operators using this equipment should critically question the easy-to-obtain data they gather. Fourth, as has happened for CT scans, age- and disease-appropriate MBW outcome measures should be validated in a systematic way (12). Those could be moment ratios (being less dependent on breathing pattern), functional residual capacity (showing the resting lung volume), or slope III analyses. Finally, imaging modalities without radiation exposure, and above all, magnetic resonance imaging, need to be included as outcome measures in early CF lung disease and compared with MBW (16).

For clinical practice, the importance of CT scans and MBW measurements lies in excluding structural or functional impairment and tracking possible treatment responses at an early age. Although annual CT scans seem less suited for routine clinical follow-up, the current study provides novel insight into the prevalence and interrelation of pulmonary structure and function in early CF lung disease. Yet we cannot conclude that either technique, MBW or CT, can replace the other over the whole pediatric age range. Nevertheless, the scene is set to formulate important questions that need to be answered as the next steps on the way to patient-oriented and practical assessment of early CF lung disease. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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